

Docket No.: 45,394

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Schlom, et al.

Serial No.: 08/500,306

Examiner: Bansal, G.

Filed: July 10, 1995

Group: 1642

For: GENERATION OF IMMUNE RESPONSES TO PROSTATE-SPECIFIC  
ANTIGEN (PSA)

DECLARATION UNDER 37 CFR 1.131

We, Jeffrey Schlom and Dennis Panicali, hereby declare as follows:

1. We are co-inventors of the above-described application.
2. We are aware that the Examiner has cited Spitler et al. (WO95/04548). This application has an international publication date of February 16, 1995 and a U. S. Priority date of August 11, 1993. A patent issued corresponding to this PCT publication issued as U.S. Patent No. 5,925,362.
3. Prior to August 11, 1993, we had completed in the United States a recombinant pox virus expressing prostate specific antigen (PSA). Two recombinant vaccinia viruses of the Wyeth strain were prepared, vT119 and vT1001. In vT119, the PSA gene is inserted at the Hind III J insertion site (i.e., the tk gene site), whereas in vT1001, the PSA gene is inserted at the Hind III M insertion site (see pages 1-2 of "Quarterly Progress Report Contract #NO1-CB-21154-02 Production of Recombinant Vaccina Virus Expressing Prostate Specific Antigen (PSA)", attached hereto as Exhibit "A". The date of this Progress Report has been redacted but was prior to August 11, 1993.

4. We made the PSA pox constructs because we had conceived in the United States prior to August 11, 1993, the idea of using a recombinant pox viral vector having an insertion site containing a DNA segment encoding PSA operably linked to a promoter and capable of expression in a host as a cancer vaccine for people suffering from prostate cancer.

5. We conceived in the United States prior to August 11, 1993, that by administration of that pox virus expressing PSA in an individual having such prostate cancer, one would stimulate the immune system, specifically both the humoral and cellular response to PSA in such individuals. The cell-mediated response would include a cytotoxic T Lymphocyte (CTL) response.

6. Consequently, we prepared the aforementioned recombinant pox vector expressing PSA to use in that method. (See Exhibit "A").

7. As taught therein, we prepared vaccinia vectors containing the PSA gene and confirmed that vT119 expressed PSA. Then we began work on preparing a master stock. (Exhibit "A" at p.2).

8. These steps were necessary to make the viral vector in sufficient quantities, to be able to perform animal testing, which had to be performed to show that such vector was safe, before we could engage in the ultimate goal, human tests.

9. A copy of an initial work plan discussing our scientific programs that listed under "The Cancer Vaccine Program" the PSA vaccinia recombinant is attached as Exhibit "B." Other cancer vaccines that we were looking at have been redacted as has the date.

The date of the work, which was performed in the United States, is prior to August 11, 1993.

10. Thus, prior to August 11, 1993, we had conceived in the United States utilizing PSA in a recombinant pox virus vector to generate an immune response and had made such constructs. We knew from experience we had with other pox viral vectors how to administer said pox viral vector, and what an immunologically sufficient response was.

11. As shown by Exhibit "B", our ultimate goal was to use these pox virus vectors in humans.

12. Although the human testing occurred subsequent to the August 11, 1993 filing date of Spitler et al., we had generated recombinant viral vector vaccines for the prevention and treatment of prostate cancer. Spitler in contrast had not even made a PSA construct and provides no experimental results.

13. Thus, Spitler taught far less than we had already accomplished in the United States prior to its filing date.

14. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so





## QUARTERLY PROGRESS REPORT

CONTRACT # NO1-CB-21154-02

### PRODUCTION OF RECOMBINANT VACCINIA VIRUS EXPRESSING PROSTATE SPECIFIC ANTIGEN (PSA)

#### I PLASMID INSERTION VECTORS

The gene encoding prostate specific antigen (PSA) has been inserted into two of Therion's plasmid vectors for recombination into vaccinia virus. These vectors each contain the PSA gene under the transcriptional control of the vaccinia 40K promoter and the *E.coli lacZ* gene to allow selection of recombinant progeny, but differ in the vaccinia genomic insertion site and in the promoter controlling *lacZ*. The important features of the two plasmids are summarized in the table below:

Plasmid designation	Vaccinia Insertion Site	Promoter/ PSA gene	Promoter/ <i>lacZ</i> gene
pT119*	HindIII J (tk)	40K / PSA	BamF / <i>lacZ</i>
pT1001	HindIII M	40K / PSA	C <sub>1</sub> / <i>lacZ</i>

\*provided by NCI as "pAbT4537PSA"

#### II GENERATION OF RECOMBINANT VIRUSES

The plasmid vector pT119 was used to generate recombinant virus in the Wyeth vaccine strain background. Three independent isolates, designated vT119 A, B and C, were purified using a colorimetric assay for  $\beta$ -galactosidase performed on viral plaques *in situ*. Recombinant viruses, which coexpress  $\beta$ -galactosidase and the PSA gene, appear blue in the presence of a histochemical substrate for the enzyme (BluoGal). Blue plaques are picked, re-plated, and are again treated with BluoGal. After seven rounds of plaque purification, all progeny plaques were blue, indicating purity of each recombinant virus stock. Viral plaque size was small, and plaques were heterogeneous with respect to levels of *lacZ* expression. This heterogeneity and the number of rounds of plaque purification required for recombinant purification were very unusual in our experience with generating vaccinia recombinants. Therefore, we undertook the generation of an

alternative recombinant using plasmid pT1001, described above. Recombinant plaques have been isolated and purification of recombinants, designated vT1001, is underway. vT1001 recombinants will be compared to vT119 recombinants with respect to plaque size, virus yield, and PSA expression. Based on the results of these analyses, one of the two recombinants will be selected for the manufacture of clinical grade material.

### III. ANALYSIS OF RECOMBINANT VIRUSES

Recombinant viruses vT119A, B and C were analyzed with respect to genomic structure by Southern analysis using PSA-specific and vaccinia-specific probes. PSA protein expression was analyzed by Western analysis using polyclonal antibodies specific for PSA. The results were identical for the three isolates: each recombinant genome contains the PSA gene inserted into the vaccinia HindIII J region, as expected, and each recombinant expresses PSA. Details of these analyses are given in the report on Genomic and Protein Expression Analysis dated

Genomic and protein analysis of alternative recombinant vT1001, discussed above, is expected to be completed by

If this recombinant is judged superior to vT119 for product manufacture, details of genomic and protein expression analysis will be submitted to NCI. Production of a Master Virus Stock for vaccine manufacture will begin in January. All work is on schedule.

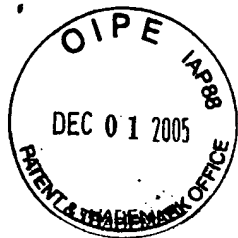


EXHIBIT "B"

C. PSA/vaccinia

1. Generation and analysis of virus seed stock
2. Product manufacture
3. Testing/final reports
4. Master file preparation





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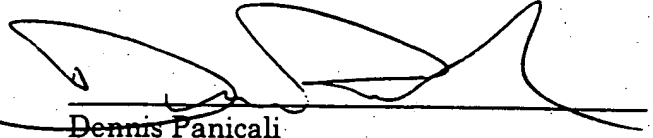
made are punishable by fine or imprisonment, and that such willful false statements may jeopardize the validity of the application or any patent that issues therefrom.

\_\_\_\_\_  
Date

4-19-00

\_\_\_\_\_  
Date

\_\_\_\_\_  
Jeffrey Schlom



\_\_\_\_\_  
Dennis Panicali

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## Prime/boost vaccination using poxviruses expressing PSA in D0 prostate cancer: preliminary results of ECOG 7897, a randomized phase II clinical trial.

Abstract No: 12

**Author(s):** Howard L Kaufman, Wei Wang, Judith Manola, Robert S DiPaola, Young-Jee Ko, Steven D Williams, Theresa Whiteside, Jeff Schlom, George Wilding, Louis M Weiner, Albert Einstein College of Medicine, Bronx, NY; Dana-Farber Cancer Inst, Boston, MA; Cancer Institute of New Jersey, New Brunswick, NJ; Beth Israel Deaconess Medcl Ctr, Boston, MA; Indiana University Medical Center, Indianapolis, IN; University of Pittsburgh, Pittsburgh, PA; National Cancer Institute, Bethesda, MD; University of Wisconsin, Madison, WI; Fox Chase Cancer Center, Philadelphia, PA.

**Abstract:** Recombinant vaccinia virus expressing prostate specific antigen (PSA) elicited anti-PSA immunity and biochemical responses in a small subset of patients with metastatic prostate cancer. In order to improve the effectiveness of this vaccine, a heterologous prime and boost approach was adopted using PSA-expressing vaccinia virus (rV) and the non-replicating fowlpox virus (rF) in patients with hormone dependent PSA progression after local therapy. The major study objectives were to evaluate the effect of the prime/boost strategy on PSA progression and toxicity in a randomized, limited multi-institutional clinical trial. The study was designed to detect a 30% progression-free rate from a 5% rate at 6 months after treatment. Seventy patients were randomized to receive four injections of rF, one rV vaccination followed by three rF vaccines (rV/rF), or three rF vaccines followed by a single rV vaccine (rF/rV), each administered every 6 weeks. The median age was 70. Toxicity was minimal with grade 1-2 injection site reaction being the most common side effect. Eleven of 64 patients eligible for analysis (17.2%) experienced progressive disease without significant differences between treatment arms. 34 of the 64 patients (53.1%) were free of PSA progression and 50 of 64 (78.1%) were free of clinical disease progression at 6 months. The median time to PSA progression was 9.2 months for the rF arm, 9.7 months for the rF/rV arm, and has not yet

been reached for the rV/rF arm. All patients are alive with a median follow-up time of 14.7 months. Vaccination with recombinant PSA vaccines is safe and, in this trial, encouraging durations of freedom from biochemical or clinical progression were observed, particularly with combined rF/rV vaccinations. These results warrant evaluation of those novel treatment approaches in Phase III trials. Additional insights will be provided by an ongoing evaluation of PSA-specific immunity. These results support further clinical trials designed to optimize the therapeutic effectiveness of vaccines targeting PSA for prostate cancer.

#### Associated Presentation(s):

**1. Prime/boost vaccination using poxviruses expressing PSA in D0 prostate cancer: preliminary results of ECOG 7897, a randomized phase II clinical trial.**

Event: 2002 ASCO Annual Meeting

Presenter: Howard L. Kaufman, MD

Session: Biologic and Targeted Therapies



#### Other Abstracts in this Sub-Category:

**1. A phase 2 trial to evaluate the efficacy of recombinant idiotypic vaccines in untreated follicular non-Hodgkin's lymphoma in the "watch-and-wait" period**

Meeting: 2002 ASCO Annual Meeting Abstract No: 13 First

Author: John Timmerman

**2. A phase I study of sequential vaccinations with fowlpox-CEA (6D)-Tricom (B7/ICAM/LFA3) alone, and in combination with vaccinia-CEA (6D)-Tricom and GM-CSF in patients with CEA expressing carcinomas**

Meeting: 2002 ASCO Annual Meeting Abstract No: 24 First

Author: John L Marshall

**3. Adjuvant treatment with monoclonal antibody, OvaRex MAb-B43.13 (OV) targeting CA125, induces robust immune responses associated with prolonged time to relapse (TTR) in a randomized, placebo-controlled study in patients (pts) with advanced epithelial ovarian cancer (EOC)**

Meeting: 2002 ASCO Annual Meeting Abstract No: 31 First

Author: Thomas G Ehlen

**4. Phase I trial of progenipoetin (SD-9427) with MART/gp100/tyrosinase peptides/IFA for resected stages III/IV melanoma**

Meeting: 2002 ASCO Annual Meeting Abstract No: 43 First

Author: Jeffrey S Weber

5. **A phase I/II trial of bystander GVAX cancer vaccine in non-small cell lung cancer (NSCLC)**

Meeting: 2002 ASCO Annual Meeting    Abstract No: 48    First  
Author: John J Nemunaitis

6. **Vaccination of metastatic melanoma patients with the autologous heat-shock protein peptide complex-96 (HSPPC-96; Oncophage) which contains melanoma peptides, results in a specific T-cell response and clinical response**

Meeting: 2002 ASCO Annual Meeting    Abstract No: 49    First  
Author: Giorgio Parmiani

7. **Immunization of HLA-A2+ melanoma patients with MelanA peptide-pulsed PBMC + rhIL-12**

Meeting: 2002 ASCO Annual Meeting    Abstract No: 60    First  
Author: Thomas F Gajewski

8. **An autologous large multivalent immunogen (LMI) vaccine for the treatment of metastatic melanoma and renal cell carcinoma**

Meeting: 2002 ASCO Annual Meeting    Abstract No: 76    First  
Author: Ian Okazaki

9. **Custom-made idiotype immunotherapies produced by high throughput gene expression technology (Hi-GET<sup>TM</sup>) for follicular non-Hodgkin's lymphoma (f-NHL) patients**

Meeting: 2002 ASCO Annual Meeting    Abstract No: 77    First  
Author: Lori A Kunkel

10. **Randomized evaluation of 3 treatment schedules to optimize clinical activity of OvaRex® MAb-B43.13 (OV) in patients (pts) with epithelial ovarian cancer (EOC)**

Meeting: 2002 ASCO Annual Meeting    Abstract No: 80    First  
Author: Michael W Method



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## Company News

### Therion Announces Oral Presentation of Clinical Data on Its Cancer Therapy PROSTVAC-VF at ASCO

**- Therion's prime/boost regimen results in favorable clinical response with stable PSA scores at 50 months -**

**ORLANDO, Fla. and CAMBRIDGE, Mass., May 14, 2005** – Therion Biologics Corporation announces the presentation of Phase II data from its PROSTVAC®-VF program for the targeted treatment of patients with prostate cancer at the 2005 American Society of Clinical Oncology (ASCO) meeting, being held May 14-18, 2005. The presentation detailed follow-up clinical results at 50 months from ECOG 7897, a trial conducted by the Eastern Cooperative Oncology Group (ECOG). The data favored Therion's prime/boost regimen using vaccinia expressing PSA (rV-PSA) followed by fowlpox expressing PSA (rF-PSA) and collectively suggest that men with hormone-dependent prostate cancer and rising PSA may derive long-term clinical benefit from vaccinations with poxviruses expressing PSA.

The oral presentation of abstract number 4501 titled, "Phase II prime/boost vaccination using poxviruses expressing PSA in hormone-dependent prostate cancer: Follow-up clinical results from the ECOG 7897" was given on Saturday, May 14th at 11:15AM by Howard L. Kaufman, M.D. of Columbia University, New York.

"These follow-up results are extremely promising with the majority of subjects in all treatment arms remaining free of disease progression and exhibiting stable PSA scores at 50 months," commented Dr. Kaufman on behalf of the Eastern Cooperative Oncology Group. "Collectively, these results establish the feasibility of a therapeutic cancer vaccine strategy for men with early hormone-dependent prostate cancer recurrences, and we believe that they support the advancement of Therion's PROSTVAC-VF program into Phase III studies."

"The persistent trend at 50 months with PSA and clinical response favoring patients receiving a prime/boost regimen represents the third confirmation of our dosing strategy for our targeted cancer therapies," commented Thomas J. Schuetz, M.D., Ph.D., Chief Medical Officer of Therion. "These data not only suggest the superiority of our favored prime/boost regimen over the other vaccine strategies used in this study, but they also continue to support the safety profile of our targeted cancer therapy platform."

**About the study:**

ECOG 7897 is an ongoing Phase II clinical trial for the evaluation of a prime/boost vaccine strategy using vaccinia virus and fowlpox virus expressing human PSA in patients with hormone-dependent prostate cancer. Sixty-four eligible patients with biochemical (PSA) progression after local therapy were randomly assigned to three treatment arms: (A) rF-PSA by intramuscular injection every six weeks for four doses, (B) rF-PSA for three doses followed by rV-PSA given by intradermal injection, or (C) rV-PSA followed by three rF-PSA vaccines. The patients enrolled in this trial have been followed for PSA response and clinical outcome for a period of 50 months to date. Vaccination was well tolerated. The median time to PSA progression is 9.2 and 9.1 months for arms A and B respectively, compared to 18.2 months for arm C. The median time to clinical progression has still not been reached for any treatment group with 80% of men in arms A and B free of disease progression compared to 90% of men in arm C free of clinical progression.

In addition to the study detailed in today's announcement, data on Therion's PANVAC-VF and PROSTVAC-VF programs for pancreatic and prostate cancer respectively will be highlighted in the following upcoming oral presentations and poster sessions:

**Oral Presentations:**

Abstract 2405

J. Gulley (NCI) Monday

May 16 (7:45 am – 10:45 am)

Developmental Therapeutics: Immunotherapy

**Poster Sessions:**

Abstract 2576

T. Schuetz (Therion)

Sunday, May 15 (8:00 am – 12:00 pm)

Developmental Therapeutics: Immunotherapy

**Abstract 2518**

P. Arlen (NCI)

Tuesday, May 17 (8:00am – 12:00 pm)

Developmental Therapeutics: Immunotherapy

Therion will also have a booth (# 1413) at ASCO to educate and recruit oncologists for late-stage studies on the Company's product candidates.

**About PROSTVAC®-VF**

PROSTVAC-VF is a targeted cancer therapy designed to stimulate a patient's own immune system to seek out and destroy cancer cells expressing epitopes (antigenic peptide sequences) of PSA found in prostate cancer. PROSTVAC-VF is designed to introduce the genes for PSA and TRICOM™ (B7.1, ICAM-1 and LFA-3) —a proprietary triad of costimulatory molecules essential for maximizing the antitumor cellular immune response— into a patient's existing antigen-presenting cells. This stimulates the activation and proliferation of an array of cytotoxic T cells, which seek out and destroy cancer cells bearing any of the targeted epitopes. PROSTVAC-VF is currently in a Phase II trial for the treatment of patients with asymptomatic androgen-independent prostate cancer.

**About Therion Biologics Corporation**

Therion Biologics Corporation is a leader in the development of novel

targeted cancer therapeutics designed to selectively seek out and destroy malignant cells without the serious side effects associated with cytotoxic chemotherapy. The company has two lead product candidates:

- PANVAC-VF is in a Phase III registration trial for the treatment of pancreatic cancer;
- PROSTVAC-VF is in Phase II trials for the treatment of prostate cancer.

In addition to these lead product candidates, clinical trials evaluating Therion's innovative targeted therapeutics in colorectal, ovarian, breast and lung cancers are also ongoing or planned. Therion's strategic partners are the National Cancer Institute (NCI) and a network of renowned clinical institutions.

Therion's technology platform has been evaluated over a 13-year period in more than 30 clinical trials comprising close to 1000 patients, chiefly through the company's longstanding partnership with the NCI. This extensive research has enabled Therion to clinically optimize its technology and maximize the probability for downstream success. Therion's two lead product candidates, PANVAC-VF and PROSTVAC-VF, are a direct result of these efforts.

For more information, please visit [www.therion.com](http://www.therion.com).

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